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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/669,176	ALITALO ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *3-5 and 14-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application 10/669,076 filed on Sep. 23, 2003 is a Continuation-In-Part of U.S. application numbers 10/262,538 filed on Sep. 30, 2002, which claims benefit of provisional application 60/326,323 filed on Oct. 1, 2001. The publication number of this application 10/669,076 is US 2004/0214766 A1, published on Oct. 28, 2004.

Status of claims: Claims 1-36 are pending.

Election/Restriction

1. In response to the Restriction Requirement mailed on March 27, 2006, Applicants elected with traverse on the facsimile transmission dated April 27, 2006 to prosecute the inventions of Group II (claims 1-2(in part), 6-10, 11-14 (in part)). It is noted that in applicants' response, it states "Applicants elect, with traverse, Group II, claims 1-2, 3-5, 11-14, drawn to methods of administrating a VEGF-C or VEGF-D polynucleotide" (page 8 lines 9-20). However, claims 3-5 are listed in the Group I (Restriction Requirement mailed on March 27, 2006, page 2). Accordingly, claims 3-5 are withdrawn from further consideration and claims 6-10 are examined.

Applicants argued "withdrawal of the Restriction between Group I, V, and VII and the restriction between groups II, VI, and VIII". Each of the methods of Group VI and VII requires an additional product (See page 8, second paragraph, Restriction Requirement). The searches for these additional products are not co-extensive with the searches for VEGF-C or VEGF-D polynucleotide. Therefore, the restriction between Group II, VI and VIII is still deemed proper.

Applicants also argued "the division of making a cell population, the cells themselves, and the methods for using the cells (e.g. Groups III and IV and claim 14) be withdrawn". These arguments are found persuasive and therefore, claim 15 (Group III), claims 16-22 (Group IV) and claim 14 are withdrawn from further consideration.

Applicant's election with traverse of Group II in the reply filed on September 23, 2003 is acknowledged. The traversal is on the ground(s) that (1) administration of a polypeptide or a polynucleotide encoding the polypeptide are related and (2) one additional agent added to a composition does not place an undue burden on the examiner to examine a second factor together. This is not found persuasive because (1) polypeptide and polynucleotide are structurally and functional distinct, and administration of each requires different considerations; and (2) as discussed in Restriction Requirement (page 8) and reasons listed above, the search for an additional agent (a neural growth factor in Group VI, a neurotherapeutic agent in Group VII) is not co-extensive with the search for the first agent, namely VEGF-C or VEGF-D polynucleotide.

Accordingly, claims 3-5, 14, 15, 16-22, 23-28, 29-31, 32-34, 35, and 36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to the nonelected inventions, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejection – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-2, 6-10, and 11-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of

experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

First, claimed invention encompasses a method of promoting recruitment, proliferation, differentiation, migration or survival of neuronal cells or neuronal precursor cells in a mammalian subject comprising administration to the subject a composition comprising a VEGF-C product or a VEGF-D product, wherein the composition is delivered via any route. Thus, the breadth of claims 1-2 and 6-10 encompasses any route of administration to deliver VEGF-C polynucleotide or VEGF-D polynucleotide to the subject.

The specification defines "the administration that is performed according to the present invention may be performed using any medically-accepted means for introducing a therapeutic directly or indirectly into a mammalian subject, including but not limited to injections (e.g., intravenous, intramuscular, subcutaneous, intracranial or catheter); oral ingestion; intranasal or topical administration; and the like" (See lines 1-5, page 74). For administration to a subject with neuronal disease, various routes are contemplated including direct injection at the site of lesion or affected tissue needing treatment, or via a sustained delivery or sustained release mechanism, which can deliver the formulation internally (See lines 5-13, page 74). The specification is not enabling for the delivery of VEGF-C or VEGF-D to a mammalian subject by any route because distinct neuronal diseases will require different considerations with regard to

the method and the site of delivery. The following are reasons why claims 1-2, and 6-10 as stated fail to comply the enablement requirement.

The specification, while being contemplated that, for instance, "the adenoviral vector is administrated multiple times on any of the days after onset of disease symptoms, to maintain a constant level of VEGF-C protein at the site of neuropathology" (See lines 20-23, page 102, instant application, 10/669,176), does not reasonably provide enablement for any possible route of administration. Relevant to the routes of administration issue, it is stated that "The adenoviral vectors are administrated either i.v. (intra-venously), i.p. (intra-peritoneally), sub-cutaneously, intra-cranially or locally at the site of nervous system trauma" (See lines 9-12, page 102, instant application, 10/669,176). In the absence of specific and explicit descriptions of detailed conditions required for successful administration of VEGF-C or VEGF-D polynucleotide for each of the possible routes designed for a given neurological disease, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification explicitly contemplates various routes of administration and ways of contacting the lesion site in neuropathology. However, the specification provides no guidance at all as to (1) how to direct the delivery of compositions to the intended site other than by administration directly to that site, and (2) how to establish a sustained delivery or sustained release mechanism, which can deliver the formulation internally. The expressed VEGF-C or VEGF-D proteins are cellular proteins, and not diffusible products, so the nucleic acids encoding them must be delivered to the cells at sites where the proteins are required. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites

continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. (Miller and Vile, Targeted vectors for gene therapy, *FASEB J.* 9(2): 190-9, 1995) reviewed the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Deonarain, Ligand-targeted receptor-mediated vectors for gene delivery, *Exp. Opin. Ther. Patents* 8(1): 53-69, 1998; Ashley Publications Ltd. ISSN 1354-3776) reviewed ligand-targeted receptor mediated vectors, and indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviewed techniques under experimentation in the art which showed promise, but which are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (Verma and Somia, Gene therapy -- promises, problems and prospects, *Nature* 389: 239-42, 1997) reviewed various vectors known in the art for use in gene therapy and the problems that are associated with each. Verma clearly indicated that resolution to vector targeting problems had not been achieved in the art (see entire article). Verma discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242). Crystal (Crystal, Transfer of genes to humans: early lessons and obstacles to success, *Science* 270: 404-10, 1995) also reviewed

various vectors known in the art and indicated, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Pouton et al. (Pouton and Seymour, Key issues in non-viral gene delivery, *Adv Drug Deliv Rev.* 46(1-3): 187-203, 2001) reviewed the issues in non-viral gene delivery and stated that "direct injection of gene medicines into target tissue represents a far simpler task than targeting delivery to a specific tissue from the systemic circulation". See last full sentence on page 188, right column, and section 2.1. Pouton et al. added that there were "no systems yet available for efficient tissue targeting following systemic delivery." (See page 189, first sentence of section 2.2.). Finally, Read et al (Read et al., Barriers to gene delivery using synthetic vectors, *Adv Genet.* 53: 19-46, 2005) stated after the time the invention was filed that the "lack of suitable vectors for the delivery of nucleic acids... represents a major hurdle to their continued development and therapeutic application" (see abstract, sentence bridging pages 19 and 20. Problem areas included obtaining persistence in the circulation, gaining access to target cells, and distinguishing target cells from non-target cells. See e.g. page 22).

The specification as filed fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation. In view of the state of the art, the unpredictability in the art, and the lack of guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to use the claimed invention

to improve lesions of neuropathology at sites other than those to which the nucleic acid sequences encoding VEGF-C or VEGF-D were directly delivered.

Second, the breadth of claims 11-13 encompasses any *in vitro* step required for isolation and purification of neural stem cell, including neural embryonic stem cells and neural adult stem cells, from a mammalian subject. The specification states, for instances, "The biological sample is subjected to purification and/or isolation procedures to purify or isolate the stem cells before the contacting step. In a related aspect, the method further comprises a step of purifying and isolating the neural stem cells or neural cells after the contacting step" (See lines 12-15, page 25); and " stem cells from the neural retina express the markers previously shown for brain-derived stem cells, GD2 ganglioside, CD15, and tetraspanins CD9 and CD81 (lines 3-5, page 26). The specification is not enabling for any step required for isolation and/or purification of neural stem cells from various tissues or organs from a mammalian subject

For claims 11-13, the basis of this rejection focuses on the method for obtaining mammalian neutral stem cells is not routine and will require specific guidance with regard to, for instances, isolation of the cells, growth conditions, maintenance at an undifferentiated stage or a desired differentiated stage, stimuli required to direct various differentiation pathways, and analysis of marker expression specific to different developmental stages. The terms "obtaining a biological sample from a mammalian subject, wherein said sample comprises neural stem cells" in claim 11, "culturing the stem cells in a culture containing VEGF-C product or VEGF-D product" stated in claim 12, and "comprising a step of purifying and isolating the neural stem cells " stated in claim 13 do not comply with the enablement requirement. The following are reasons why claims 11-13 as stated fail to comply the enablement requirement.

The specification, while being stated that, for instances, "neural stem cells found in adult mammals are isolated primarily from hippocampus, olfactory bulb and adult ventricular zone, as well as the spiral cord" (See lines 14-15, page 50, instant application), "Neural stem cells can be induced to differentiate into any neural cells including glia, oligodendrocytes, neurons, or astrocytes" (See lines 1-2, page 50, instant application), and "VEGF-C product or VEGF-D product is administrated to cells in culture to stimulate proliferation of the stem cells themselves, or to induce differentiation of a desired population of neural cell, which is then transplanted into the individual in need of therapy" (See lines 4-7, page 53, instant application) do not reasonably provide enablement for (1) the possible sources of neural stem cells from various tissues of a given mammal species, with which the VEGF-C and VEGF-D will contact (2) the detailed conditions, for example including the concentrations of VEGF-C or VEGF-D and the processes of ascertaining the genomic stability and expression of distinct, neural specific marker genes, in the purified and isolated neural stem cells that are to be treated with VEGF-C or VEGF-D, and (3) the correlations between treatment with VEGF-C or VEGF-D and stages of differentiation of the treated neural stem cells.

Supporting the arguments for the abovementioned issues regarding lack of enablement in claims 11-13 in the instant application, Odorico et al. reviewed the properties of human embryonic stem cells, multilineage differentiation of the stem cells both *in vitro* and *in vivo* (Odorico et al., Multilineage differentiation from human embryonic stem cell lines, *Stem Cells* 19(3): 193-204, 2001). Odorico et al. documented the complexities involved in isolation and purification of embryonic stem cells from human

The specification as filed fails to teach any specific techniques for isolation and purification of neural stem cells, fails to provide any working examples which encompass explicitly detailed conditions for treatment of neural stem cells with VEGF-C or VEGF-D, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation. In view of the state of the art, the unpredictability in the art, and the lack of guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to use the claimed invention to treat neural stem cells by VEGF-C or VEGF-D to stimulate differentiation of the neural stem cells to a stage bearing desired characteristics for intended uses, for instance, transplantation of the treated neural stem cells into a different mammalian subject.

Third, the breadth of claim 6 encompasses any polynucleotide sequences that are at least 90% identical to either nucleotide sequences SEQ ID NO: 23 encoding a polypeptide that binds VEGFR-3 or a nucleotide sequence that encodes the human VEGF-C amino acid sequence SEQ ID NO: 24. The length of sequences defining "at least 90% identical to" do not necessarily to be full length of either nucleotide sequences SEQ ID NO: 23 encoding a polypeptide that binds VEGFR-3 or a nucleotide sequence that encodes the human VEGF-C amino acid sequence SEQ ID NO: 24. Furthermore, claim 6 encompasses any polynucleotide that hybridizes to the complement sequences of SEQ ID NO: 23 under defined stringent conditions, which include washing with 0.1X SSC/0.1% SDS 15 min at 55^0C.

For claim 6, the basis of this rejection focuses on the undefined polynucleotide sequences with at least 90% identical to nucleotide sequences of SEQ ID No: 23 (claim 6c), or nucleotide

sequences that encodes a polypeptide comprising an amino acid sequences with at least 90% identical to SEQ NO: 24 (claim 6d), wherein the polypeptide binds VEGFR-3. In the absence of clarification on the exact locations and identities of nucleotides or amino acids that consist of the remaining 10% sequence deviations from SEQ ID 24 or SEQ ID NO 23, the possible sequences that meet the limitation stated in the claim "at least 90% identical to" SEQ ID NO: 24 or 23 are indefinite. For instance, a calculation on possible numbers of deviated SEQ ID NO: 24 (419 amino acid residues) that have 10% (41 amino acid residues) non-identical sequences of SEQ ID NO: 24 will give 19^{41} (i.e. 2.68×10^{52}) distinctive combinations when only D or L form of 20 different amino acids are considered. In this regard, the specification does not provide explicit guidance in term of (1) how this huge number of different molecules will be generated and (2) how these molecules will be analyzed for their function(s) in the context of binding to VEGFR-3 and triggering activation/repression of the target genes downstream of the signaling pathway. Furthermore, generation of a specific polynucleotide library of extremely large scale and performing required functional assays of the peptide encoded by the library are not a routine practice of any skilled person in the art and require detailed and explicit guidance and undue experimentation.

In view of the lack of guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to use the claimed invention of polynucleotide sequences encoding VEGF-C products that binds to VEGFR-3 as stated in claim 6.

Claim Rejection – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-2, 6-10, and 11-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Moore et al (U.S. patent application publication No. 2001/0021700 A1; publication date Sep. 13, 2001).

Moore et al. teach, primarily, 49 novel human secreted proteins and administration of isolated nucleic acids encoding the polypeptides. With regard to claims 1, 2, 6-10, Moore et al. also teach administration of polynucleotides encoding other angiogenic proteins, which promote cell growth and proliferation, including VEGF-C (See for examples, page 82, paragraph 0644, and page 121, paragraph 1058) and VEGF-D (See for example, page 121, paragraph 1058), along with administration of polynucleotides encoding the 49 human secreted proteins for diagnosing and treating disease, disorders, and/or conditions related to those novel human secreted proteins (See abstract; claims 17, a method for preventing, treating , or ameliorating a medical condition, comprising administrating to a mammalian subject a therapeutically effective amount of ---; claims 18 and 19, a method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising ---).

With regard specific to claims 6 and 7 on the binding of VEGF-C or fragment thereof to VEGFR-3, the inherent prosperities of VEGF-C and VEGF-D anticipate the binding of these two growth factors to their receptors VEGFR-2 and VEGFR-3.

With regard to claims 11-13, Moore et al. further teach *in vitro* examination of the dopaminergic neuronal cells, which are prepared by dissecting midbrain floor plate from gestation day 14 Wistar rat embryos, in response to the treatment of growth factor (See page 130, example 35, paragraph 1146).

It is noted that in the instant application, the terms "neural stem cell", "neuronal progenitor cell", "neuronal cell", "neuronal precursor cell", and "neurosphere" are used interchangeably (See paragraph 00178 on page 19, instant application, publication number US 2004/0214766 A1). The term "dopaminergic neuronal cells" stated by Moore et al. as abovementioned is considered as a specific species of the term "neuronal cells" defined by the applicants of instant application (See lines 28-30, page 51, instant application).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-2, 6-10, and 11-13 are also rejected under 35 U.S.C. 102(e) as being anticipated by Delfani et al (U.S. patent application number 10/246,091, patent application publication No.

2003/0203844 A1, publication date Oct. 30, 2001; filed date Sep. 18, 2002; effective filing date Sep. 28, 2001).

Delfani et al. teach the invention relates generally to methods of influencing central nervous cells to produce progeny useful in the treatment of CNS disorders. The invention includes methods of exposing a patient suffering from such as disorder to a reagent that modulates the proliferation, migration, differentiation and survival of central nervous system cells (See Abstract, patent application publication No. 2003/0203844 A1).

More specifically, Defani et al. teach (1) with regard to claims 1-2 and 6-10, a method for accelerating the growth of a neural stem cells or neural progenitor cells in a desired target tissue in a subject, comprising administrating intramuscularly to the subject an expression vector containing a PDGF or VEGF gene in a therapeutic effective amount (See page 36, claim 58), (2) with regard to claims 11-13, a method of exposing neural stem cells or neural progenitor cells to exogenous reagent (including VEGF-C and VEGF-D), wherein the exposure induces the neural stem cells or neural progenitor cells to proliferate or differentiate (page 35, claims 18 and 21), and (3) with regard specific to claims 6 and 7 on the binding of VEGF-C or fragment thereof to VEGFR-3, a method of modulating a VEGF receptor (including VEGFR-3, which is also named as Flt-4) on a neural stem cell, comprising exposing the cell expressing the receptor to exogenous reagent, wherein the exposure induces the neural stem cell to proliferate or differentiate. The reagent includes VEGF-C and VEGF-D (See page 3, paragraph 0019; pages 33-34, example 11).

Therefore, the teachings of Delfani et al. anticipate the invention of claims 1-2, 6-10, and 11-13.

Obviousness-type double patenting rejection

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 6-10, and 11-13 of instant application U.S. 10/669,173 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6, 12, 20, 22- 27, and 38 of the other U.S. application of copending Application No. 10/868,577. The assignee of both application numbers 10/669,173 and 10/868,577 is LICENTIA, LTD.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-2, 6-10, and 11-13 of instant application U.S. 10/669,173 are drawn to a method of promoting recruitment, proliferation, differentiation, migration or survival of neuronal cells in a mammalian subject and a method of stimulating neural stem cell proliferation of differentiation whereas claims 1, 4, 6, 12, 20, 22- 27, and 38 of the U.S. application number 10/868,577 are drawn to a method of stimulating angiogenesis, which promote cell growth and proliferation, in a mammal comprising transforming or transfecting a cell with a polynucleotide that encodes a polypeptide binds VEGFR-2 (for instance, as stated in claim 4). It is worth noting that both VEGF-C and VEGF-D bind both VEGFR-2 and VEGFR-3 (See, for example, a review by Veikkola et al.) (Veikkola et al., Regulation of angiogenesis via vascular endothelial growth factor receptors. *Cancer Res.* 60(2): 203-12, 2000).

Furthermore, the inventors of application U.S. 10/868,577 also teach the polypeptide derived from VEGF-C or VEGF-D expressed by a polynucleotide from a vector is administrated to neural stem cells to a patient with a neurodegenerative disorder or neural trauma (See page 4, paragraph 0044, patent application publication No US 2005/0032697 A1).

Therefore, claims 1-2, 6-10, and 11-13 of instant application U.S. 10/669,176 are not patentably distinct from claims 1, 4, 6, 12, 20, 22- 27 and 38 of the U.S. 10/868,577. In light of

the U.S. 10/868,577 application, clarification on the inventorship of the claims in the instant application is required

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

6. No claim is allowed.

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Ram Shukla, can be reached on (571) 272-0735. The fax number for TC 1600 is (571) 273-8300. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632